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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/294,298	04/19/99	HUGANIR	R 48235

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/294,298	HUGANIR ET AL.	
	Examiner	Art Unit	
	Karen Clemens	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *6/28/99, 8/10/00 and 11/27/00* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32,34,35,44,45,48,54,56 and 62-69* is/are pending in the application.

4a) Of the above claim(s) *22-24,26-28,31,32,34,35,44,45,48,54,56 and 62-69* is/are withdrawn from consideration.

5)☒ Claim(s) *2* is/are allowed.

6)☒ Claim(s) *1, 3-21, 25 and 29-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/14/00* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Claims 1-32, 34-35, 44-45, 48, 54, 56 and 62-69 are currently pending.

2. Applicant's election of Group I, claims 1-21, 25 and 29-30 in Paper No. 11, dated 11/27/00 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

3. Upon reconsideration the prior art search has been extended to include the A, B, and C species of SYNGAP.

4. Claims 22-24, 26-28, 31-32, 34-35, 44-45, 48, 54, 56 and 62-69 are withdrawn from further consideration by the Examiner as being drawn to nonelected inventions (see 37 C.F.R. 1.142(b)).

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(h).

6. Claims 1-21, 25 and 29-30 are under examination.

7. Drawings have been submitted which fail to comply with 37 C.F.R.1.84. Please see the enclosed form PTO-948.

8. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

A. Claim 1, 3-21, 25 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to an isolated polynucleotide encoding a mammalian Synaptic GTPase Activating Protein (SYNGAP) wherein the SYNGAP has a molecular weight of between about 100 to 140 kD, has at least about 70 percent sequence identity to SEQ ID NO:1, 3 or 5, is in the form of a kit, is a cDNA or RNA, is of human origin, is a fragment or derivative of the polynucleotide, said fragment or derivative cloned into a recombinant vector contained in a host cell where the polypeptide is produced, or is an isolated polynucleotide in a kit comprising a sequence with at least about 70% sequence homology to SEQ ID NO:1, 3 or 5, or a pair of oligonucleotide primers in a kit capable of hybridizing to the sequence shown in any one of SEQ ID NO:1, 3 or 5 under high stringency conditions. The claims are further drawn to an isolated polynucleotide that is capable of hybridizing to any one of the sequences shown in SEQ ID NO:1, 3 or 5 under moderate or high stringency conditions, wherein the polynucleotide is between about 12 to about 50 or about 100 to 3500 nucleotides in length. The claims are further drawn to the said polynucleotides between about 100 to 3500 nucleotides in length wherein the polynucleotide encodes an amino acid sequence that is capable of activating Ras GTPase by at least about 20% in a standard Ras GTPase assay, and is capable of binding a PDZ domain as determined by a standard PDZ domain binding assay, and that is capable of binding an NR1 subunit of an NMDA receptor as determined by a standard NMDA receptor binding assay, and which comprises at least a RAS GTPase activating protein (GAP) domain and a C-terminus comprising the following amino acid sequence: (Tor S) X V; wherein X is an amino acid, and which the encoded polypeptide further comprises a pleckstrin homology (PH) and a C2 domain, and the encoded polypeptide comprises in an N to C terminus orientation: the pleckstrin homology domain (PH), the C2 domain, the GAP domain and the C-terminal amino acid sequence, and further comprises in an N to C terminus orientation at least about amino acids of SEQ ID NO:6 from 4 to 72, 87 to 190, 266 to 502 and 1132 to 1135, or a polynucleotide encoding a mammalian SYNGAP fragment or derivative of SEQ ID NO:2, 4 or 6.

However Applicant's disclosure is limited the polynucleotides, cDNA or RNA, of SEQ ID NO:1, 3 and 5 and polynucleotides that encode the polypeptides of SEQ ID NO:2, 4 and 6 and the polynucleotides that encode the fragments of SEQ ID NO:6 from amino acids 4 to 72, 87 to 190, 266 to 502 and 1132 to 1135.

The Applicant has not disclosed, nor does the art recognize, the genus of SYNGAP polypeptide-encoding polynucleotides in which there exists an established correlation or relationship between the

structure of the instant invention and its function, deemed essential to the instant invention. One skilled in the art would not envisage, from the instant disclosure, polynucleotides which encode polypeptides with the functions of SYNGAP (A, B and C), outside of the aforementioned nucleotides of SEQ ID NO:1, 3 and 5 and polypeptides of SEQ ID NO:2, 4 and 6. Therefore, one of skill in the art would not recognize the Applicant to be in possession of the genus of polynucleotides that encode SYNGAP polypeptides as claimed.

Consequently, the claimed invention is not described in such a way as to reasonably convey to one of ordinary skill in the art that the inventor, at the time the application was filed, had possession of the invention. See *Regents of the University of California v. Eli Lilly & Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).* Applicant is also directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

B. Claims 1, 3-21, 25 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for the polynucleotide of SEQ ID NO:1, 3 and 5 and encoding polypeptide of SEQ ID NO:2, 4 and 6 does not reasonably provide enablement for all polynucleotides encoding any mammalian Synaptic GTPase Activating Protein (SYNGAP) wherein the SYNGAP has a molecular weight of between about 100 to 140 kD, has at least about 70 percent sequence identity to SEQ ID NO:1, 3 or 5, is a cDNA or RNA, is of human origin, is a fragment or derivative of the polynucleotide, said fragment or derivative cloned into a recombinant vector contained in a host cell where the polypeptide is produced or is an isolated polynucleotide in a kit comprising a sequence with at least about 70% sequence homology to SEQ ID NO:1, 3 or 5, or a pair of oligonucleotide primers in a kit capable of hybridizing to the sequence shown in any one of SEQ ID NO:1, 3 or 5 under high stringency conditions. The specification further does not provide sufficient enablement for an isolated polynucleotide that is capable of hybridizing to any one of the sequences shown in SEQ ID NO:1, 3 or 5 under moderate or high stringency conditions, wherein the polynucleotide is between about 12 to about 50 or about 100 to 3500 nucleotides in length wherein the said polynucleotides between about 100 to 3500 nucleotides in length encodes an amino acid sequence that is capable of activating Ras GTPase by at least about 20% in a standard Ras GTPase assay, and is capable of binding a PDZ domain as determined by a standard PDZ domain binding assay, and that is capable of binding an NR1 subunit of an NMDA receptor as determined by a standard NMDA receptor binding assay, and which comprises at least a RAS GTPase activating protein (GAP) domain and a C-terminus comprising the following amino acid sequence: (Tor S) X V; wherein X is an amino acid, and which the encoded polypeptide further comprises a pleckstrin homology (PH) and a C2 domain, and the encoded polypeptide comprises in an N to C terminus orientation: the

pleckstrin homology domain (PH), the C2 domain, the GAP domain and the C-terminal amino acid sequence, and further comprises in an N to C terminus orientation at least about amino acids of SEQ ID NO:6 from 4 to 72, 87 to 190, 266 to 502 and 1132 to 1135, or a polynucleotide encoding a mammalian SYNGAP fragment or derivative of SEQ ID NO:2, 4 or 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and amount of experimentation required to enable one of skill in the art to practice the claimed invention.

There is insufficient guidance and a limited number of working examples in the specification such that one skilled in the art could practice the invention as broadly claimed without an undue amount of experimentation. Which alterations of the polynucleotides of SEQ ID NO:1, 3 and 5, that encode a polypeptide other than that encoded by SEQ ID NO:2, 4 and 6, can be made or similar sequences obtained which retain the functional properties of the SYGAP polypeptides requires a knowledge of, and guidance with regard to, which amino acid alterations, if any, are tolerant of modification and a detailed knowledge of the way in which the product's structure relates to its functional usefulness. The ability to predict the functional aspects of a protein product, and consequently the use of the product to one skilled in the art, from primary amino acid sequence data is complex and well outside the realm of routine experimentation. The current state of the art for protein structure/function prediction based on primary amino acid sequence data is currently inadequate given the multifunctional nature of proteins (see Skolnick et al., abstract in particular). Without such guidance, which nucleotide alterations can be made or polynucleotides encoding homologous polypeptides can be used and which possess the claimed biological activities is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly undue.

In view of the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, it would take an undue amount of experimentation for one skilled in the art to practice the full scope of the claimed invention.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention."

Claims 3-4, 6-10 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A. The "polypeptide" in base claim 15 has no antecedent basis in base Claim 14. Base Claim 14 only recites a polynucleotide.

B. Claims 3, 4, 8, 9 and 10 are indefinite and ambiguous in the recitation of the phrases "has a molecular weight *of between about* 100kD to about 140kD" (claim 3), "*at least about* 70% sequence identity"(claim 4), "*is between about* 12 to 50 nucleotides" (claim 8), "*is between about* 100 to about 3500 nucleotides" (claim 9), "an amino acid sequence capable of activating Ras GTPase *by at least about* 20%" (claim 10). It is unclear what specific range of molecular weight (claim 3), actual percentage of sequence identity (claim 4), the actual nucleotides encompassed by the claim (claims 8 and 9) and level of activation of Ras GTPase (claim 10) are encompassed by the claims.

C. Claims 6-7 are indefinite in the recitation of an isolated polynucleotide that is capable of hybridizing to any one of the sequences shown in SEQ ID NOs: 1, 3 or 5 under *moderate* (claim 6) or *high* (claim 7) stringency conditions. These conditions are not defined by the claims and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> "A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."

Claims 1, 3-10 and 13-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Chen et al. (Society for Neuroscience, Vol. 23, Part 2, Abstract, 27th Annual Meeting, October 25-30, 1997, 578.10).

Chen et al., teach an isolated polynucleotide encoding a mammalian Synaptic GTPase Activating Protein (SYNGAP) wherein the SYNGAP has a molecular weight of between about 100 to 140 kD, has at least about 70 percent sequence identity to SEQ ID NO:1, 3 or 5, is a cDNA of rat origin, is a fragment or derivative of the polynucleotide, and said fragment or derivative is cloned into a recombinant vector. Chen et al. further teach an isolated polynucleotide that is capable of hybridizing to any one of the sequences shown in SEQ ID NO:1, 3 or 5 under moderate or high stringency conditions, wherein the polynucleotide is between about 12 to about 50 or about 100 to 3500 nucleotides in length wherein the said polynucleotides between about 100 to 3500 nucleotides in length encodes an amino acid sequence that is capable of activating Ras GTPase by at least about 20% in a standard Ras GTPase assay, and which comprises at least a RAS GTPase activating protein (GAP) domain and a C-terminus comprising the following amino acid sequence: (Tor S) X V; wherein X is an amino acid, and which the encoded polypeptide further comprises a pleckstrin homology (PH) and a C2 domain, and the encoded polypeptide comprises in an N to C terminus orientation: the pleckstrin homology domain (PH), the C2 domain, the GAP domain and the C-terminal amino acid sequence, and further comprises in an N to C terminus orientation at least about amino acids of SEQ ID NO:6 from 4 to 72, 87 to 190, 266 to 502 and 1132 to 1135, or a polynucleotide encoding a mammalian SYNGAP fragment or derivative of SEQ ID NO:2, 4 or 6.

Therefore, the reference teachings thus anticipate the claimed invention.

12. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is

advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 21 and 25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chen et al. in view of Sambrook et al. (*Molecular Cloning*, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17).

Chen et al. has been discussed supra.

However, Chen et al. does not teach a host cell containing the expression vector and a method for producing the polypeptide comprising culturing the host cell and recovering the polypeptide from the culture.

However, Sambrook et al. teach a process of transforming the expression vector into host cells, culturing the host cells under conditions in which the polypeptide is expressed and then recovering the polypeptide from the culture (see Chapter 17, page 17.2 in particular). Sambrook et al. teach that it is desirable to use recombinant DNA techniques for the production of biologically active proteins in order to produce proteins of higher concentration and purity.

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to generate a host cell containing the said expression vector. This host cell could then be used to produce the polypeptide comprising the polynucleotides under conditions which express the polypeptide in order to recover the polypeptide from the culture as taught by the Sambrook et al. One having ordinary skill in the art at the time the invention was made would have been motivated to produce the polypeptide(s) using recombinant techniques because there would be a higher yield of polypeptide with greater purity as taught by Sambrook et al.

B. Claims 29-30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chen et al. in view of U.S. Patent 5,384,242.

Chen et al. has been discussed supra.

However, Chen et al. does not teach an isolated polynucleotide in a kit and/or a pair of oligonucleotide primers in a kit capable of hybridizing to the polynucleotide under high stringency conditions. However, the '242 Patent teaches a kit suitable for DNA amplification or detection containing a template DNA and

primers for the amplification of the target DNA following proper hybridization of the primers to the template (see abstract in particular).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to pack the template DNA and/or specific primers into a diagnostic kit as taught by the '065 Patent. One having ordinary skill in the art at the time the invention was made would have been motivated to use a diagnostic kit to isolate or detect the SYNGAP polynucleotides in samples since diagnostic kits are convenient and can be used readily in a laboratory settings (see column 1, lines 10-16 in particular).

13. Claim 2 is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Clemens whose telephone number is (703) 308-8365. The examiner can normally be reached Monday through Friday from 8:00 AM to 5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Karen Clemens, Ph.D.
Patent Examiner
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January 26, 2001

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